BUCZEK, Aleksandra, JAKUBCZYK, Paulina, BILCZEWSKA, Olga, JANIK, Wiktoria, HANDSCHUH, Marta, HELIS, Justyna, WIDERA, Piotr, BANAŚ, Aleksandra, MICHALIK, Maciej and BIGAJSKI, Hubert. The Impact of Physical Activity on Neuroprotection in Neurodegenerative Diseases: A Special Focus on Parkinson's Disease. Quality in Sport. 2024;36:56588. eISSN 2450-3118.
https://doi.org/10.12775/QS.2024.36.56588
https://apcz.umk.pl/QS/article/view/56588

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 02.12.2024. Revised: 22.12.2024. Accepted: 22.12.2024. Published: 22.12.2024.

The Impact of Physical Activity on Neuroprotection in Neurodegenerative Diseases: A Special Focus on Parkinson's Disease

Authors:
Aleksandra Buczek [1], Paulina Jakubczyk [2], Olga Bilczewska [1], Wiktoria Janik [1], Marta Handschuh [1], Justyna Helis [1], Piotr Widera [1], Aleksandra Banaś [1], Maciej Michalik [1], Hubert Bigajski [1]
Affiliations
[1] Faculty of Medical Sciences in Katowice, Medical University of Silesia
[2] University Hospital of Karol Marcinkowski in Zielona Góra

Abstract

Aim of the study

This study examines the impact of physical activity on neuroprotection in neurodegenerative diseases, focusing on Parkinson's Disease (PD). It evaluates neuroprotective mechanisms, analyzes physical activity's role in PD progression, assesses various exercise forms' effectiveness on PD symptoms, and identifies research challenges and future directions.

Materials and methods

A comprehensive literature search was conducted across major databases, prioritizing studies from the past 15 years, particularly longitudinal studies and randomized controlled trials. The review critically evaluated neuroprotective mechanisms, exercise specificity, and effects on PD symptoms.

State of knowledge

Regular physical activity enhances neuroplasticity, regulates neurotrophic factors, reduces oxidative stress, and mitigates inflammation in PD patients. Various exercise forms show effectiveness in managing PD symptoms and potentially slowing disease progression. Challenges remain in optimizing interventions for individual patients and integrating physical activity into comprehensive PD management strategies.

Conclusions
The review highlights physical activity's significant neuroprotective effects in PD, demonstrating its potential to manage symptoms and slow progression. Research gaps persist regarding long-term effects and personalized interventions. Future research should focus on optimizing exercise protocols, investigating synergistic effects with pharmacological treatments, and developing personalized interventions. This review supports physical activity as a valuable adjunctive therapy in PD, potentially influencing treatment paradigms in neurodegenerative disorders.

Keywords: “neuroprotection”, “neurodegenerative diseases”, “Parkinson’s Disease”, "BDNF", “physical activity”

1. Aim of the study

The primary objective of this review is to comprehensively examine the impact of physical activity on neuroprotection in neurodegenerative diseases, with a special focus on Parkinson's Disease (PD). This study aims to:
Evaluate the neuroprotective mechanisms activated by physical activity, including:
- Enhanced neuroplasticity
- Regulation of neurotrophic factors, particularly Brain-Derived Neurotrophic Factor (BDNF)
- Reduction of oxidative stress and inflammation

Highlight which of these mechanisms are most significant in the context of PD.
Analyze the role of physical activity in PD by:
- Briefly reviewing the neurodegenerative processes in PD
- Examining studies on the effects of exercise on PD progression
- Assessing the effectiveness of various forms of physical activity (aerobic exercises, strength training, dance, yoga) on both motor and non-motor symptoms of PD

Explore the long-term effects of exercise and its efficacy in early-stage versus advanced PD patients.
Identify challenges in current research and outline future directions, including:
- The potential synergistic action of physical activity with pharmacological therapies
- The need for personalized exercise programs for PD patients

By addressing these aims, this review seeks to provide a comprehensive understanding of the role of physical activity in neuroprotection, particularly in the context of PD, and to highlight its potential as an adjunctive therapeutic strategy in the management of neurodegenerative disorders.

2. Materials and methods

This review employs a comprehensive approach by performing a broad literature search regarding the impact of physical activity on neuroprotection in neurodegenerative diseases, with a special focus on PD. Aspects like neuroprotective mechanisms, exercise specificity, and the effects on PD symptoms were taken under consideration. Extensive searches were conducted across various databases including PubMed, Web of Science, and Google Scholar using applicable keywords: "physical activity", "exercise", "neuroprotection", "neurodegenerative diseases", "Parkinson's Disease", "neuroplasticity", "BDNF", "oxidative stress", "inflammation", "motor symptoms", and "non-motor symptoms". The analyzed data was drawn with critical evaluation of study design, participant groups, and outcomes. Additionally, relevant review articles and meta-analyses were examined to ensure a comprehensive coverage of the topic. Studies published in English within the last 15 years were prioritized. Particular attention was given to longitudinal studies and randomized controlled trials that investigated the long-term effects of various types of physical activity on PD progression and symptom management.

3. State of knowledge

3.1 PD and the Neurodegenerative Processes Involved

3.1.1 Parkinson's Disease

PD is one of the most common neurodegenerative disorders observed in current times (Balestrino and Schapira 2020; Buczek et al. 2024) . Studies suggest that its expected occurrence is projected to double in the upcoming 30 years (Tolosa et al. 2021), potentially rising to 10 million people globally by 2030 (Vijiaratnam et al. 2021). The primary characteristic of PD is a progressive decline in motor function, which significantly impacts the quality of life for those affected (Balestrino and Schapira 2020). PD is an age-progressive disease, most impactful on the elderly population, especially over 80 years of age (Hayes 2019).

The exact cause of this disease is yet to be determined. The progression of PD is marked by its slow, gradual pace, with each step of the condition taking from months to years to develop (Małgorzata Gaweł, Anna Potulska-Chromik 2015).

PD is defined by a range of motor syndromes. Those include: bradykinesia - overall reduction in movement speed and a noticeable decline in voluntary or unconscious motions. Rest tremor - typically ranging from 4 to 6 Hz, commonly observed in the limbs, but can also affect the lips, chin, or jaw, though it is less common in the head. The tremor's amplitude tends to decrease or disappear during purposeful voluntary movements. Rigidity - increased muscle tone is observed as resistance to passive movement of equal intensity in opposing muscle groups, often described as a "lead-pipe" rigidity.When this resistance is interrupted by tremor, it leads to a "cog-wheel" phenomenon. Changes in posture and gait - a tendency to drag one leg, mildly stooped posture during walking and diminished arm swing (Port et al. 2021).

These motor disturbances hinder daily functioning and lead to progressive disability. In addition to motor symptoms, patients also experience a variety of non-motor symptoms, such as constipation, memory decline, depression, sleep disturbances, urinary issues,dysphagia and hyposmia. These symptoms emerge in the early stages of the disease and become more pronounced as the condition progresses (Tolosa et al. 2021).

3.1.2 Pathogenesis

The etiopathogenesis of this disease remains still not fully understood. Currently, a range of factors are considered in the pathogenesis, including genetic factors, environmental factors, the action of free radicals, and oxidative stress (Tolosa et al. 2021). Furthermore, we can correlate the disease with a range of risk factors. According to researchers, they include:

Pesticides, Methamphetamine, Traumatic Brain Injury, Body-Mass Index (BMI) and Diabetes, Blood Cholesterol and Hypertension, Drinking alcohol, and Diets rich in polyunsaturated fats (Ascherio and Schwarzschild 2016).

One prevailing hypothesis suggests that the premature aging and degeneration of neurons within the substantia nigra ultimately lead to a diminished dopamine concentration in the striatum, subsequently being the cause of PD (Małgorzata Gaweł, Anna Potulska-Chromik 2015).

According to research, PD is a progressive neurodegenerative disorder associated with the accumulation of aggregated α-synuclein (Morris et al. 2024). α-Synuclein (ASN) is a low-molecular-weight (140-amino-acid) cytosolic protein present in the central nervous system. It has been demonstrated that this protein is one of the primary components of cytoplasmic inclusions known as Lewy bodies (Anna KAMIERCZAK, Agata ADAMCZYK, Joanna Benigna and STROSZNAJDER 2007). Lewy bodies may be detrimental to neurons as they are space-occupying lesions that can alter cellular function (Morris et al. 2024). The central centers controlling autonomic functions include the cortex, insula, hypothalamus, brainstem, and spinal cord, and both neuronal destruction and α-synuclein accumulation have been observed in these areas (Chen, Li, and Liu 2020).

Research, including studies on animal models, has shown that the abnormal structure of a single synuclein molecule, when transformed from an alpha-conformation to a beta-sheet structure, causes the remaining synuclein to also convert into the beta form and accumulate secondarily as beta-amyloid. This process leads to premature cell death. The death of substantia nigra cells, in turn, results in a decrease in dopamine levels in the striatum (Małgorzata Gaweł, Anna Potulska-Chromik 2015).

Due to the decrease in dopamine in the substantia nigra, there is a disruption in the transmission of nerve impulses, which prevents the brain from transmitting signals properly. As a result, there is a loss of connection between the brain and other parts of the body, leading to a loss of control over body movements, which constitutes the essence of PD (Chen, Li, and Liu 2020).

3.2 Neuroprotective mechanisms activated by physical activity

Physical activity is increasingly recognized for its neuroprotective effects, particularly in the context of neurodegenerative diseases such as PD (Langeskov-Christensen et al. 2024). The mechanisms through which physical activity exerts these protective effects include enhanced neuroplasticity, regulation of neurotrophic factors like BDNF, and reduction of oxidative stress and inflammation (Palasz E, Niewiadomski W, Gasiorowska A, Wysocka A, Stepniewska A, Niewiadomska G. 2019; Palasz et al. 2020). Each of these mechanisms play a crucial role in maintaining neuronal health and function.

Increased neuroplasticity is one of the primary benefits of physical activity (Zou J, Hao S 2024). Exercise promotes synaptic plasticity, which is essential for learning and memory (Mu et al. 2022). This is particularly relevant in PD, where cognitive decline is a significant concern. Studies have shown that physical activity can lead to structural and functional changes in the brain, enhancing its ability to adapt and reorganize in response to new experiences or injuries (Kleim Jeffrey A. and Jones Theresa A. 2008; Erickson et al. 2011). Neuroimaging studies have demonstrated that regular exercise correlates with increased gray matter volume in areas associated with motor control and cognition (Silvia Paola Caminiti et al. 2024).

Regulation of Neurotrophic Factors, especially BDNF, is another critical mechanism activated by physical activity. BDNF is vital for neuronal survival, growth, and differentiation.

Exercise has been shown to significantly increase BDNF levels in the brain, which supports neurogenesis and synaptic plasticity (Szuhany, Bugatti, and Otto 2015). In the context of PD, where dopaminergic neurons are progressively lost, maintaining elevated levels of BDNF may help protect existing neurons and promote the survival of new ones (Decker 2023). Furthermore, interventions that enhance BDNF signaling have been linked to improved motor function in PD models (Singh et al. 2023). Increased BDNF levels are associated with improved cognitive function and mood regulation. Physical activity stimulates the expression of the BDNF gene in various brain regions, including the hippocampus, cortex, and striatum (Jabr, Vanessa 2020; Dicarlo et al. 2023). This increase in gene expression results in higher levels of BDNF protein synthesis. During exercise, muscle contractions release myokines, such as interleukin-6 (IL-6), which can promote BDNF expression in the brain. This suggests a communication pathway between skeletal muscle and the central nervous system (Dicarlo et al. 2023).

Regular physical activity can lower stress levels and reduce cortisol production (De Nys et al. 2022). High cortisol levels can inhibit BDNF expression; thus, reducing stress through exercise may indirectly enhance BDNF levels (Ramirez 2024).

Reduction of Oxidative Stress is another important effect of physical activity. Exercise induces the production of endogenous antioxidants that combat oxidative stress, a significant contributor to neuronal damage in PD (Souza et al. 2022). By reducing oxidative damage, physical activity may help preserve dopaminergic neurons and mitigate the progression of PD symptoms (Bishop, Lu, and Yankner 2010).

Anti-Inflammatory Effects are also observed with regular physical activity. Chronic inflammation is a hallmark of neurodegenerative diseases, including PD (Hu, Huang, and Chen 2024; Palasz E, Niewiadomski W, Gasiorowska A, Wysocka A, Stepniewska A, Niewiadomska G. 2019). Exercise has been shown to reduce levels of pro-inflammatory cytokines and modulate microglial activation, thereby decreasing neuroinflammation (Mee-inta, Zhao, and Kuo 2019). This anti-inflammatory effect can further protect against neuronal loss and improve overall brain health. Regular physical activity can modulate inflammatory responses in the brain. It reduces the activation of microglia, the immune cells of the central nervous system, which can become overactive in neurodegenerative diseases. By decreasing neuroinflammation, exercise may help protect against neuronal damage associated with conditions like PD.

In summary, while all these mechanisms contribute to the neuroprotective effects of physical activity, the regulation of BDNF levels and the reduction of oxidative stress are particularly significant in the context of PD. The ability of exercise to enhance BDNF signaling not only supports neuronal survival but also promotes neuroplasticity, both critical for combating the cognitive and motor deficits associated with PD.

3.3 The Impact of Exercise on PD Progression

PD is the second most common neurodegenerative condition, but its underlying risk factors are not well understood. While laboratory studies indicate that physical activity might have a protective effect on the brain, there is limited research exploring whether being physically active reduces the risk of developing the disease (Logroscino et al. 2006).

Physical exercise has positive effects on mitigating central nervous system degeneration by modulating the glutamatergic and dopaminergic systems. Additionally, the therapeutic benefits of exercise are linked to its role in regulating autophagy, apoptosis, inflammation, α-synuclein aggregation, and mitochondrial function (Feng et al. 2020).

The effectiveness of exercise in patients with Parkinsonian syndrome varies based on the stage of the condition, but it offers benefits in both early and advanced stages (Mitchell, Bliss, and Church 2024). In the early stages of PD, exercise can help delay the worsening of motor symptoms, enhance flexibility and strength, and improve overall physical health. It promotes neuroplasticity, which may safeguard motor abilities and contribute to better quality of life. Engaging in physical activity early on also aids in maintaining balance, improving coordination, and enhancing mobility, enabling individuals to retain their independence for longer periods (Padilha et al. 2023; Mitchell, Bliss, and Church 2024). In the advanced stages of PD, exercise plays a key role in addressing motor symptoms like stiffness, slowness of movement (bradykinesia), and difficulty with balance and posture. It helps minimize the risk of falls, enhances walking ability, and supports the maintenance of remaining physical functions. Additionally, physical activity can improve mental well-being by reducing symptoms of anxiety and depression, which are often prevalent in advanced stages of the disease (Mitchell, Bliss, and Church 2024).

The long-term effects of exercise on people with PD are widely recognized, offering benefits for both motor and non-motor symptoms (Maher et al. 2024). Research indicates that incorporating aerobic, resistance, and balance-oriented exercises can foster neuroplasticity, helping preserve neural pathways and potentially mitigating the effects of neurodegeneration in PD. These long-term changes can enhance quality of life and slow the progression of disability. Exercise routines that are carefully tailored to an individual's abilities and the stage of their disease tend to yield the most significant benefits over time (M. K. Mak et al. 2017).

3.4 How Different Types of Exercise Affect Motor and Non-Motor Symptoms in PD

Physical activity can be categorized into several types, including aerobic exercise, strength training, stretching, and balance and coordination exercises (Filar-Mierzwa et al. 2021). Each type provides distinct benefits, making them particularly valuable for individuals with PD (Moratelli et al. 2024).

Regular physical activity, particularly aerobic training, provides numerous benefits for patients with PD. It helps reduce symptoms such as hypokinesia, bradykinesia, and gait disturbances, slows neuronal degeneration, supports independence in activities of daily living (ADL), and enhances cardiovascular fitness, especially in individuals with mild to moderate stages of the disease (Padilha et al. 2023).

Aerobic exercise has been shown to enhance functional connectivity between the anterior putamen and the sensorimotor cortex relative to the posterior putamen, as well as improve cognitive control. Additionally, it has contributed to strengthening connectivity within the right frontoparietal network in proportion to increases in physical fitness and has reduced global brain atrophy (Johansson et al. 2022).

Aerobic exercise, also referred to as cardio or endurance training, is a category of physical activity that engages large muscle groups and increases heart rate and breathing in a manner that ensures an adequate supply of oxygen to the muscles during the activity (Prieto-González and Yagin 2024). The exercise is characterised by a moderate intensity and longer duration, which facilitate the combustion of calories, enhance cardiovascular fitness, and fortify the respiratory system. Examples of aerobic exercises include walking, running, swimming, cycling, dancing, and aerobics (Bhalsing, Abbas, and Tan 2018; Prieto-González and Yagin 2024). For individuals diagnosed with PD, participation in aerobic training has been demonstrated to confer substantial benefits, with improvements observed in both motor and non-motor symptoms. It has been demonstrated to enhance cardiovascular fitness, muscle strength, and balance, thereby mitigating issues such as gait disturbances and rigidity (Zhou et al. 2022; M. K. Y. Mak and Wong-Yu 2021). Regular aerobic exercise has been demonstrated to enhance motor control, reduce bradykinesia and enhance overall mobility (M. K. Y. Mak and Wong-Yu 2021). Furthermore, it has been demonstrated that aerobic exercise can enhance neuroplasticity, which may potentially lead to a slowing of disease progression by promoting the release of BDNF, which is known to support neural health (Petzinger et al. 2013). In addition, aerobic training has been demonstrated to reduce fatigue, improve mood, and alleviate symptoms of depression and anxiety, thereby enhancing the quality of life of individuals with PD (Altmann et al. 2016).

Strength training, also known as resistance training, is a category of physical activity designed to increase muscle strength, endurance and mass (Brienesse and Emerson 2013). The practice of strength training involves performing exercises that require muscles to work against a resistance, which may include the use of weights, resistance bands, one's own body weight, or specialised machines (Paolucci et al. 2020). Strength training provides a wide range of benefits for people with PD. Increasing muscle strength and stability helps to reduce tremor and improve mobility, thereby improving motor function (Kelly et al. 2014). Strengthening the core and lower body muscles has also been shown to improve balance and posture, reducing the risk of falls (Paolucci et al. 2020). Strength training is an effective way to promote functional independence by improving strength and endurance, which are essential for performing daily activities (M. K. Y. Mak and Wong-Yu 2019). From a neurological perspective, it has been shown to increase dopamine release and promote neuroplasticity, which can have a positive effect on mood and cognitive function (Petzinger et al. 2013).

Flexibility exercises are activities that are specifically designed to enhance the range of motion and flexibility of muscles and joints (M. K. Y. Mak and Wong-Yu 2019). These exercises comprise static stretching, which involves maintaining a position for a specified duration, and dynamic stretching, which encompasses controlled movements through the full range of motion of a joint (Sharma et al. 2015; Behm and Chaouachi 2011). Examples of flexibility exercises include yoga, pilates, stretching on a mat or in water, or dance classes such as jazz and ballet (Kwok et al. 2019; Skelton DA, Mavroeidi A 2018). These exercises enhance range of motion by reducing rigidity, facilitating smoother and more efficient movement (M. K. Y. Mak and Wong-Yu 2019).They also improve posture and alignment, which contributes to enhanced balance and coordination, reducing the risk of falls (Boulgarides, Barakatt, and Coleman-Salgado 2014). Increased joint flexibility supports greater mobility, facilitating easier and less painful everyday activities such as walking and reaching (King and Horak 2009). Additionally, stretching can relieve the muscle cramps and discomfort often experienced in PD, while promoting relaxation and mental well-being (Colgrove et al. 2012).

Balance and coordination exercises confer a number of advantages, including enhanced stability, improved posture, injury prevention, elevated athletic performance, and augmented confidence in daily movements. (Mak & Wong-Yu, 2019) Examples of such exercises include yoga poses such as the Tree Pose, Tai Chi, walking heel-to-toe, and dance styles such as ballroom or salsa. (Hackney & Earhart, 2008) + (Li et al., 2012)

Balance and coordination exercises are of significant benefit to those with PD, as they address key motor symptoms such as postural instability, rigidity, and bradykinesia (Kim et al. 2013). Such exercises have been demonstrated to enhance stability, reduce the risk of falls, and improve mobility, thereby facilitating safer and more manageable performance of daily activities (López-Liria et al. 2023; Liu et al. 2019). Furthermore, they enhance proprioception (body awareness) and neuromuscular coordination, which are frequently compromised in individuals with PD (Rinalduzzi et al. 2015).

Both conventional training and exercises utilizing virtual reality (VR) effectively reduce the severity of motor symptoms in patients with early and mid-stage PD, confirming the efficacy of available rehabilitation methods. Additionally, gait training incorporating augmented reality (AR) and VR allows for the gradual improvement of walking skills through task performance under increasingly challenging conditions, supporting motor learning while enhancing balance and gait quality. These findings highlight the potential of modern technologies to complement traditional rehabilitation approaches (Gulcan et al. 2023).

Dance is a form of activity that involves synchronizing movements with musical rhythm, combining various physical, cognitive, emotional, and social aspects. Research suggests that performing complex sensorimotor tasks activates the medial geniculate nucleus, which may contribute to improvements in both motor and non-motor functions in the course of this disease (Ismail et al. 2021).

Tai Chi training demonstrates a long-lasting beneficial effect on both motor and non-motor symptoms in patients with PD, improving gait, balance, sleep, and cognitive functions, among others. The results suggest that regular practice of Tai Chi may provide significant therapeutic benefits, and that consistent continuation of the exercises aids in more effective symptom management (Li et al. 2024).

Research suggests that water-based training has a significant positive effect on quality of life, whereas endurance training and exercises targeting gait and balance have a somewhat lesser impact (Ernst and Kalbe 2023).

3.5 Synergistic Action of Physical Activity and Pharmacological Therapies in PD

The synergistic interplay between physical activity and pharmacological therapies has emerged as a compelling complementary approach for managing neurodegenerative diseases, particularly PD (Dibble et al. 2015). This interaction represents a promising strategy to enhance clinical outcomes by targeting multiple aspects of disease pathology and symptom management.Physical activity has been shown to induce neuroplastic changes and modulate the dopaminergic system, potentially augmenting the therapeutic effects of pharmacological agents. Additionally, this synergy may amplify the benefits of interventions through improved drug metabolism, reduced side effects, and augmented physiological effects.

Preclinical models reveal that exercise promotes dopamine release and receptor sensitivity, which may amplify the pharmacodynamic effects of drugs like levodopa (Vučcković et al. 2010; Bastioli et al. 2022).

While existing evidence highlights the potential of combined interventions, further research is necessary to optimize their implementation, particularly by evaluating how exercise can synergize with emerging therapies, such as deep brain stimulation or gene therapies, to enhance overall outcomes.

Studies have shown that combining physical activity with other emerging therapeutic modalities, such as transcranial direct current stimulation (tDCS), can yield synergistic benefits for cognitive and motor functions in PD patients (Beretta et al. 2020). However, the optimal parameters for these combined interventions remain unclear. Future research should aim to determine the most effective types, intensities, and durations of physical activity that can be integrated with pharmacological treatments to maximize therapeutic outcomes (Bacanoiu et al. 2020).

3.6 The Diverse Presentation and Progression of PD and the Need for Personalized Exercise Programs

The diverse presentation and progression of (PD) necessitate the development of personalized exercise programs tailored to the individual needs and capacities of patients. This need for personalization is based on several critical factors including disease stage, symptom profile, comorbidities, and the patient's overall physical fitness.

PD manifests differently across individuals, not only in terms of severity but also in symptom types, rate of progression, and response to treatment. As a result, a "one-size-fits-all" approach to exercise is unlikely to be effective. Studies have highlighted the importance of considering individual variations when designing exercise programs to ensure that they are both safe and effective (Almikhlafi 2023).

The progression of PD involves both motor and non-motor symptoms that change over time. In the early stages of the disease, patients may still exhibit relatively mild motor symptoms and can benefit from high-intensity aerobic training, which has been shown to enhance motor performance and cognitive function (Ou et al. 2021; Ramirez 2024). However, as the disease progresses and motor symptoms worsen, the focus of exercise interventions may shift toward fall prevention, improving gait and balance, and maintaining independence in activities of daily living. Personalized exercise interventions based on disease stage may also address non-motor symptoms, such as depression and cognitive dysfunction, which can vary widely among PD patients.

Patients with PD often present with comorbidities such as cardiovascular disease, osteoarthritis, or diabetes, which can impact their ability to participate in exercise (King et al. 2014). Personalization of exercise programs must therefore account for these comorbid conditions. For instance, individuals with significant cardiovascular or pulmonary disease may need lower-intensity, longer-duration exercise regimens to avoid undue strain, while those with musculoskeletal limitations may benefit from strength training or flexibility exercises rather than aerobic activities. Understanding the interplay between PD and these comorbidities is crucial to creating safe and effective exercise prescriptions.

3.7 Challenges and future directions

1. General Limitations of Scientific Research

a. Heterogeneity of Study Samples

PD exhibits considerable variability in symptoms and progression, complicating the homogeneity of study groups. Altmann et al. (2016) note that differences in age, sex, and disease duration can significantly affect research outcomes. Similarly, Liu et al. (2019) demonstrated that demographic diversity limits the generalizability of study findings. A meta-analysis by Padilha et al. (2023) confirmed that small sample sizes in studies reduce statistical power, particularly hampering conclusions about the effectiveness of various therapies.

b. Difficulty in Generalizing Results

The diversity of therapeutic approaches, such as yoga, Tai Chi, aerobic, or resistance training, makes it challenging to apply findings to all PD patients. For example, Filar-Mierzwa et al. (2021) focused exclusively on older women, limiting the applicability of results to other populations.

c. Short-Term Nature of Studies

Most studies assess the short-term effects of exercise. Johansson et al. (2022) conducted a study showing changes in brain function due to aerobic interventions but lacked long-term evaluations of this method's effectiveness. Similarly, Colgrove et al. (2012) found that short intervention durations hindered the assessment of therapeutic effects' durability.

d. Lack of Standardized Research Protocols

The absence of uniform guidelines on intensity, frequency, and methods for measuring therapeutic outcomes presents a significant challenge. As Balestrino and Schapira (2020) observed, differences in research protocols complicate comparing results and forming consistent clinical recommendations.

2. Selected Research Challenges

a. Methodological Challenges

1. Neuroplasticity as an Intervention Outcome

Studies like those by Petzinger et al. (2013) and Kleim & Jones (2008) emphasize the need for advanced technologies (MRI, PET) to assess neuroplasticity. The cost of these tools limits their accessibility, particularly for smaller research centers.

2. Evaluation of Non-Motor Symptoms

Moratelli et al. (2024) pointed out that many studies focus on motor symptoms, neglecting non-motor aspects like depression, apathy, or sleep disorders. The lack of tools tailored to assess these symptoms restricts comprehensive analyses of therapy effects on patients' quality of life.

b. Diversity in Mechanisms of Therapy Action

Therapeutic mechanisms such as neuroprotection, reduced neuroinflammation, or improved neuroplasticity vary depending on the type of exercise. Bastioli et al. (2022) demonstrated that different training protocols activate distinct biological pathways, complicating the development of unified therapeutic recommendations.

c. Long-Term Adaptation of Patients

Mak and Wong-Yu (2019) highlight that patients may struggle to maintain regular physical activity over extended periods, negatively affecting the sustainability of therapeutic outcomes.

d. Variable Pharmacological Interactions

Exercise can interact with dopaminergic medications, complicating efficacy evaluations. Dibble et al. (2015) found that combining pharmacological therapy with physical activity potentially enhances treatment outcomes, though this requires further investigation.

3. Suggestions for Improvements

- Standardization of Research: Establishing unified exercise protocols and assessment methods will enable better comparisons of results across studies (Balestrino & Schapira, 2020).
- Long-Term Cohort Studies: Longer study durations will better evaluate the impact of therapies on disease progression. Mak and Wong-Yu (2021) suggest that prolonged interventions could yield more lasting effects.
- Interdisciplinary Approaches: Combining physical, pharmacological, and psychological therapies may produce more comprehensive outcomes (Padilha et al., 2023).
- Application of Technology: Advanced tools, such as wearable devices, could help monitor therapy progress (Gulcan et al., 2023).

4. Conclusions

4.1 Synthesis of Key Findings

This comprehensive review has illuminated the significant impact of physical activity on neuroprotection in neurodegenerative diseases, with a special focus on PD. The research demonstrates that regular physical activity can enhance neuroplasticity, regulate neurotrophic factors (particularly BDNF), reduce oxidative stress, and mitigate inflammation in PD patients. These mechanisms collectively contribute to the preservation of neuronal health and function, potentially slowing disease progression.

Various forms of exercise, including aerobic training, strength training, flexibility exercises, and specialized programs like dance therapy, have shown varying degrees of effectiveness in managing PD symptoms and potentially slowing disease progression. Aerobic exercise, in particular, has demonstrated improvements in functional connectivity in the brain and cognitive control.

4.2 Research Gaps and Future Directions

Despite promising results, several research gaps remain:

1. Long-term effects: While short-term benefits are well-documented, the long-term neuroprotective effects of physical activity in PD require further investigation.
2. Personalized interventions: Given the diverse presentation and progression of PD, there is a pressing need for personalized exercise programs tailored to individual patient needs, considering factors such as disease stage, symptom profile, and comorbidities.
3. Synergistic effects: Further research is needed to optimize the synergistic action of physical activity with pharmacological therapies and emerging treatments like deep brain stimulation.
4. Standardization of protocols: Future studies should aim to standardize exercise protocols, considering intensity, frequency, duration, and type of activity to enhance comparability across studies.

4.3 Implications and Significance

The findings of this review underscore the potential of physical activity as a valuable adjunctive therapeutic strategy in the management of PD. The neuroprotective mechanisms activated by exercise offer a non-pharmacological approach to potentially slow disease progression and improve quality of life for PD patients.

The demonstrated benefits of various exercise modalities on both motor and non-motor symptoms of PD highlight the importance of incorporating physical activity into comprehensive PD management strategies. This holistic approach, combining tailored exercise programs with traditional pharmacological treatments, may offer improved outcomes for patients across different stages of the disease.

4.4 Final Thoughts

As research in this field progresses, it is crucial to address the identified challenges and pursue the outlined future directions. By doing so, we can enhance our understanding of

the neuroprotective effects of physical activity in PD and develop more effective, personalized interventions. This continued research effort holds the promise of significantly improving the lives of individuals affected by PD and potentially other neurodegenerative disorders.
The findings presented in this review not only contribute to the advancement of knowledge in the field but also provide a strong foundation for future research. They underscore the importance of physical activity as a complementary approach in PD management and highlight the need for continued investigation to optimize its therapeutic potential.

Authors' Contributions Statement:

- Conceptualization: Aleksandra Buczek
- Data Curation: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska, Wiktoria Janik, Marta Handschuh, Justyna Helis, Piotr Widera, Aleksandra Banaś, Maciej Michalik, Hubert Bigajski
- Formal Analysis: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska, Wiktoria Janik, Marta Handschuh, Justyna Helis, Piotr Widera, Aleksandra Banaś
- Investigation: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska, Wiktoria Janik, Marta Handschuh, Justyna Helis, Maciej Michalik, Hubert Bigajski
- Methodology: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska
- Project Administration: Aleksandra Buczek, Paulina Jakubczyk, Hubert Bigajski
- Resources: Olga Bilczewska, Wiktoria Janik, Marta Handschuh, Justyna Helis, Piotr Widera
- Software: Olga Bilczewska, Wiktoria Janik, Marta Handschuh
- Supervision: Aleksandra Buczek, Paulina Jakubczyk, Hubert Bigajski
- Validation: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska, Wiktoria Janik, Marta Handschuh, Justyna Helis, Piotr Widera, Aleksandra Banaś, Maciej Michalik, Hubert Bigajski
- Visualization: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska, Wiktoria Janik, Marta Handschuh, Justyna Helis, Piotr Widera, Aleksandra Banaś, Maciej Michalik, Hubert Bigajski
- Writing – Original Draft: Aleksandra Buczek, Paulina Jakubczyk , Olga Bilczewska, Wiktoria Janik, Marta Handschuh
- Writing – Review & Editing: Justyna Helis, Piotr Widera, Aleksandra Banaś, Maciej Michalik, Hubert Bigajski

All authors have reviewed and consented to the publication of the final version of the manuscript.

Conflict of Interest Statement: The authors declare no conflicts of interest.

Funding Statement: This study did not receive any specific funding.

Informed Consent Statement: Not applicable.

Ethics Committee Statement: Not applicable.

Almikhlafi, Mohannad A. 2023. "The Role of Exercise in Parkinson's Disease." *Neurosciences Journal* 28 (1): 4. https://doi.org/10.17712/nsj.2023.1.20220105.

Altmann, Lori J.P., Elizabeth Stegemöller, Audrey A. Hazamy, Jonathan P. Wilson, Dawn Bowers, Michael S. Okun, and Chris J. Hass. 2016. "Aerobic Exercise Improves Mood, Cognition, and Language Function in Parkinson's Disease: Results of a Controlled Study." *Journal of the International Neuropsychological Society* 22 (9): 878–89. https://doi.org/10.1017/S135561771600076X.

Anna KAMIERCZAK, Agata ADAMCZYK, Joanna Benigna and STROSZNAJDER. 2007. "THE INFLUENCE OF α-SYNUCLEIN ON DOPAMINERGIC SYSTEM FUNCTION" 34 (2).

Ascherio, Alberto, and Michael A Schwarzschild. 2016. "The Epidemiology of Parkinson's Disease: Risk Factors and Prevention." *The Lancet Neurology* 15 (12): 1257–72. https://doi.org/10.1016/S1474-4422(16)30230-7.

Bacanoiu, Manuela V., Radu R. Mititelu, Mircea Danoiu, Gabriela Olaru, and Ana M. Buga. 2020. "Functional Recovery in Parkinson's Disease: Current State and Future Perspective." *Journal of Clinical Medicine* 9 (11). https://doi.org/10.3390/jcm9113413.

Balestrino, R., and A.H.V. Schapira. 2020. "Parkinson Disease." *European Journal of Neurology* 27 (1): 27–42. https://doi.org/10.1111/ene.14108.

Bastioli, Guendalina, Jennifer C. Arnold, Maria Mancini, Adam C. Mar, Begoña Gamallo-Lana, Khalil Saadipour, Moses V. Chao, and Margaret E. Rice. 2022. "Voluntary Exercise Boosts Striatal Dopamine Release: Evidence for the Necessary and Sufficient Role of BDNF." *The Journal of Neuroscience* 42 (23): 4725. https://doi.org/10.1523/JNEUROSCI.2273-21.2022.

Behm, David G., and Anis Chaouachi. 2011. "A Review of the Acute Effects of Static and Dynamic Stretching on Performance." *European Journal of Applied Physiology* 111 (11): 2633–51. https://doi.org/10.1007/s00421-011-1879-2.

Beretta, Victor Spiandor, Núbia Ribeiro Conceição, Priscila Nóbrega-Sousa, Diego Orcioli-Silva, Luana Karla Braz Fonseca Dantas, Lilian Teresa Bucken Gobbi, and Rodrigo Vitório. 2020. "Transcranial Direct Current Stimulation Combined with Physical or Cognitive Training in People with Parkinson's Disease: A Systematic Review." *Journal of NeuroEngineering and Rehabilitation* 17 (1): 74. https://doi.org/10.1186/s12984-020-00701-6.

Bhalsing, Ketaki S., Masoom M. Abbas, and Louis C. S. Tan. 2018. "Role of Physical Activity in Parkinson's Disease." *Annals of Indian Academy of Neurology* 21 (4). https://journals.lww.com/annalsofian/fulltext/2018/21040/role_of_physical_activity_in_parkinson_s_disease.3.aspx.

Bishop, Nicholas A., Tao Lu, and Bruce A. Yankner. 2010. "Neural Mechanisms of Ageing and Cognitive Decline." *Nature* 464 (7288): 529–35. https://doi.org/10.1038/nature08983.

Boulgarides, Lois, Edward Barakatt, and B Coleman-Salgado. 2014. "Measuring The Effect Of An Eight-Week Adaptive Yoga Program On The Physical And Psychological Status Of Individuals With Parkinson's Disease. A Pilot Study." *International Journal of Yoga Therapy* 24 (September):31–41. https://doi.org/10.17761/ijyt.24.1.377526054663236k.

Brienesse, Laura A., and Michael N. Emerson. 2013. "Effects of Resistance Training for People With Parkinson's Disease: A Systematic Review." *Journal of the American Medical Directors Association* 14 (4): 236–41. https://doi.org/10.1016/j.jamda.2012.11.012.

Buczek, Aleksandra, Michał Borończyk, Patrycja Hudzińska, Hubert Bigajski, Alicja Białas, Wiktoria Balcerzak, Klaudia Marcinkiewicz, Jakub Milczarek, and Joanna Siuda. 2024. "Risk Factors for Falls in Parkinson's Disease and Other Parkinsonisms."

Archives of Gerontology and Geriatrics Plus 1 (4): 100054. https://doi.org/10.1016/j.aggp.2024.100054.
Bytowska, Zofia K., Daria Korewo-Labelle, Konrad Kowalski, Witold Libionka, Katarzyna Przewłócka, Wojciech Kloc, and Jan J. Kaczor. 2023. "Impact of 12 Weeks of Vitamin D3 Administration in Parkinson's Patients with Deep Brain Stimulation on Kynurenine Pathway and Inflammatory Status." *Nutrients* 15 (17). https://doi.org/10.3390/nu15173839.
Chen, Zhichun, Guanglu Li, and Jun Liu. 2020. "Autonomic Dysfunction in Parkinson's Disease: Implications for Pathophysiology, Diagnosis, and Treatment." *Neurobiology of Disease* 134 (February):104700. https://doi.org/10.1016/j.nbd.2019.104700.
Colgrove, Yvonne, Neena Sharma, Patricia Kluding, Debra Potter, Kayce Imming, Jessica VadeHoef, Jill Stanhope, Kathleen Hoffman, and Kristin White. 2012. "Effect of Yoga on Motor Function in People with Parkinson's Disease: A Randomized, Controlled Pilot Study." *Journal of Yoga & Physical Therapy* 2 (May). https://doi.org/10.4172/2157-7595.1000112.
Crowley, Erin K., Yvonne M. Nolan, and Aideen M. Sullivan. 2018. "Neuroprotective Effects of Voluntary Running on Cognitive Dysfunction in an α-Synuclein Rat Model of Parkinson's Disease." *Neurobiology of Aging* 65 (May):60–68. https://doi.org/10.1016/j.neurobiolaging.2018.01.011.
Cusso, Melanie E., Kenneth J. Donald, and Tien K. Khoo. 2016. "The Impact of Physical Activity on Non-Motor Symptoms in Parkinson's Disease: A Systematic Review." *Frontiers in Medicine* 3. https://doi.org/10.3389/fmed.2016.00035.
De Nys, Len, Kerry Anderson, Esther F. Ofosu, Gemma C. Ryde, Jenni Connelly, and Anna C. Whittaker. 2022. "The Effects of Physical Activity on Cortisol and Sleep: A Systematic Review and Meta-Analysis." *Psychoneuroendocrinology* 143 (September):105843. https://doi.org/10.1016/j.psyneuen.2022.105843.
Decker, Kevin. 2023. "Nutritional Strategies for the Exercise-Induced Increases in Brain-Derived Neurotrophic Factor." *The Journal of Physiology* 601 (11): 2217–18. https://doi.org/10.1113/JP284482.
Dibble, Leland E., K. Bo Foreman, Odessa Addison, Robin L. Marcus, and Paul C. LaStayo. 2015. "Exercise and Medication Effects on Persons With Parkinson Disease Across the Domains of Disability: A Randomized Clinical Trial." *Journal of Neurologic Physical Therapy* 39 (2). https://journals.lww.com/jnpt/fulltext/2015/04000/exercise_and_medication_effects_on_persons_with.2.aspx.
Dicarlo, Manuela, Patrizia Pignataro, Roberta Zerlotin, Clelia Suriano, Chiara Zecca, Maria T. Dell'Abate, Giuseppina Storlino, et al. 2023. "Short-Term Irisin Treatment Enhanced Neurotrophin Expression Differently in the Hippocampus and the Prefrontal Cortex of Young Mice." *International Journal of Molecular Sciences* 24 (11). https://doi.org/10.3390/ijms24119111.
Erickson, Kirk I., Michelle W. Voss, Ruchika Shaurya Prakash, Chandramallika Basak, Amanda Szabo, Laura Chaddock, Jennifer S. Kim, et al. 2011. "Exercise Training Increases Size of Hippocampus and Improves Memory." *Proceedings of the National Academy of Sciences* 108 (7): 3017–22. https://doi.org/10.1073/pnas.1015950108.
Ernst, M, Folkerts, A-K, Gollan, R, Lieker, E, Caro-Valenzuela, J, Adams, A, Cryns, N, Monsef, I, Dresen, A, Roheger, M, Eggers, C, Skoetz, N, and E Kalbe. 2023. "Physical Exercise for People with Parkinson's Disease: A Systematic Review and Network Meta-analysis." *Cochrane Database of Systematic Reviews*, no. 1. https://doi.org/10.1002/14651858.CD013856.pub2.

Feng, Ya-Shuo, Si-Dong Yang, Zi-Xuan Tan, Man-Man Wang, Ying Xing, Fang Dong, and Feng Zhang. 2020. “The Benefits and Mechanisms of Exercise Training for Parkinson’s Disease.” *Life Sciences* 245 (March):117345. https://doi.org/10.1016/j.lfs.2020.117345.

Filar-Mierzwa, Katarzyna, Małgorzata Długosz-Boś, Anna Marchewka, and Paulina Aleksander-Szymanowicz. 2021. “Effect of Different Forms of Physical Activity on Balance in Older Women.” *Journal of Women & Aging* 33 (5): 487–502. https://doi.org/10.1080/08952841.2020.1718579.

Garcia, P. C., C.C. Real, and L.R. Britto. 2017. “The Impact of Short and Long-Term Exercise on the Expression of Arc and AMPARs During Evolution of the 6-Hydroxy-Dopamine Animal Model of Parkinson’s Disease.” *Journal of Molecular Neuroscience* 61 (4): 542–52. https://doi.org/10.1007/s12031-017-0896-y.

Gulcan, Kubilay, Arzu Guclu-Gunduz, Evren Yasar, Ulas Ar, Yesim Sucullu Karadag, and Fettah Saygili. 2023. “The Effects of Augmented and Virtual Reality Gait Training on Balance and Gait in Patients with Parkinson’s Disease.” *Acta Neurologica Belgica* 123 (5): 1917–25. https://doi.org/10.1007/s13760-022-02147-0.

Hayes, Michael T. 2019. “Parkinson’s Disease and Parkinsonism.” *The American Journal of Medicine* 132 (7): 802–7. https://doi.org/10.1016/j.amjmed.2019.03.001.

Hood, Rebecca L., William A. Liguore, Cynthia Moore, Lacey Pflibsen, and Charles K. Meshul. 2016. “Exercise Intervention Increases Spontaneous Locomotion but Fails to Attenuate Dopaminergic System Loss in a Progressive MPTP Model in Aged Mice.” *Brain Research* 1646 (September):535–42. https://doi.org/10.1016/j.brainres.2016.06.032.

Hu, Junhui, Baiqing Huang, and Kang Chen. 2024. “The Impact of Physical Exercise on Neuroinflammation Mechanism in Alzheimer’s Disease.” *Frontiers in Aging Neuroscience* 16. https://api.semanticscholar.org/CorpusID:272119804.

Ismail, Sophia Rasheeqa, Shaun Wen Huey Lee, Dafna Merom, Puteri Sofia Nadira Megat Kamaruddin, Min San Chong, Terence Ong, and Nai Ming Lai. 2021. “Evidence of Disease Severity, Cognitive and Physical Outcomes of Dance Interventions for Persons with Parkinson’s Disease: A Systematic Review and Meta-Analysis.” *BMC Geriatrics* 21 (1): 503. https://doi.org/10.1186/s12877-021-02446-w.

Jabr, Vanessa. 2020. “Autophagy Mediates the Effects of Physical Exercise on Learning and Memory through Activation of Hippocampal BDNF,” July. https://doi.org/10.26756/th.2022.302.

Johansson, Martin E., Ian G. M. Cameron, Nicolien M. Van der Kolk, Nienke M. de Vries, Eva Klimars, Ivan Toni, Bastiaan R. Bloem, and Rick C. Helmich. 2022. “Aerobic Exercise Alters Brain Function and Structure in Parkinson’s Disease: A Randomized Controlled Trial.” *Annals of Neurology* 91 (2): 203–16. https://doi.org/10.1002/ana.26291.

Kelly, Neil A., Matthew P. Ford, David G. Standaert, Ray L. Watts, C. Scott Bickel, Douglas R. Moellering, S. Craig Tuggle, et al. 2014. “Novel, High-Intensity Exercise Prescription Improves Muscle Mass, Mitochondrial Function, and Physical Capacity in Individuals with Parkinson’s Disease.” *Journal of Applied Physiology* 116 (5): 582–92. https://doi.org/10.1152/japplphysiol.01277.2013.

Keus, Samyra H.J., Marten Munneke, Maarten J. Nijkrake, Gert Kwakkel, and Bastiaan R. Bloem. 2009. “Physical Therapy in Parkinson’s Disease: Evolution and Future Challenges.” *Movement Disorders* 24 (1): 1–14. https://doi.org/10.1002/mds.22141.

Kim, Samuel D., Natalie E. Allen, Colleen G. Canning, and Victor S. C. Fung. 2013. “Postural Instability in Patients with Parkinson’s Disease.” *CNS Drugs* 27 (2): 97–112.

https://doi.org/10.1007/s40263-012-0012-3.
King, Laurie A, and Fay B Horak. 2009. “Delaying Mobility Disability in People With Parkinson Disease Using a Sensorimotor Agility Exercise Program.” *Physical Therapy* 89 (4): 384–93. https://doi.org/10.2522/ptj.20080214.
King, Laurie A., Kelsey C. Priest, John Nutt, Yiyi Chen, Zunqiu Chen, Marsha Melnick, and Fay Horak. 2014. “Comorbidity and Functional Mobility in Persons with Parkinson Disease.” *Archives of Physical Medicine and Rehabilitation* 95 (11): 2152–57. https://doi.org/10.1016/j.apmr.2014.07.396.
Kleim Jeffrey A. and Jones Theresa A. 2008. “Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage.” *Journal of Speech, Language, and Hearing Research* 51 (1): S225–39. https://doi.org/10.1044/1092-4388(2008/018).
Kwok, Jojo Y. Y., Jackie C. Y. Kwan, M. Auyeung, Vincent C. T. Mok, Claire K. Y. Lau, K. C. Choi, and Helen Y. L. Chan. 2019. “Effects of Mindfulness Yoga vs Stretching and Resistance Training Exercises on Anxiety and Depression for People With Parkinson Disease: A Randomized Clinical Trial.” *JAMA Neurology* 76 (7): 755–63. https://doi.org/10.1001/jamaneurol.2019.0534.
Langeskov-Christensen, Martin, Erika Franzén, Lars Grøndahl Hvid, and Ulrik Dalgas. 2024. “Exercise as Medicine in Parkinson’s Disease.” *Journal of Neurology, Neurosurgery & Psychiatry* 95 (11): 1077. https://doi.org/10.1136/jnnp-2023-332974.
Lau, Yuen-Sum, Gaurav Patki, Kaberi Das-Panja, Wei-Dong Le, and S. Omar Ahmad. 2011. “Neuroprotective Effects and Mechanisms of Exercise in a Chronic Mouse Model of Parkinson’s Disease with Moderate Neurodegeneration.” *European Journal of Neuroscience* 33 (7): 1264–74. https://doi.org/10.1111/j.1460-9568.2011.07626.x.
Li, Gen, Pei Huang, Shishuang Cui, Yachao He, Yuyan Tan, and Shengdi Chen. 2024. “Effect of Long-Term Tai Chi Training on Parkinson’s Disease: A 3.5-Year Follow-up Cohort Study.” *Journal of Neurology, Neurosurgery & Psychiatry* 95 (3): 222. https://doi.org/10.1136/jnnp-2022-330967.
Liu, Hsin-Hsuan, Nai-Chen Yeh, Yi-Fan Wu, Yea-Ru Yang, Ray-Yau Wang, and Fang-Yu Cheng. 2019. “Effects of Tai Chi Exercise on Reducing Falls and Improving Balance Performance in Parkinson’s Disease: A Meta-Analysis.” *Parkinson’s Disease* 2019 (1): 9626934. https://doi.org/10.1155/2019/9626934.
Logroscino, G, H D Sesso, R S Paffenbarger, and I-M Lee. 2006. “Physical Activity and Risk of Parkinson’s Disease: A Prospective Cohort Study.” *Journal of Neurology, Neurosurgery & Psychiatry* 77 (12): 1318. https://doi.org/10.1136/jnnp.2006.097170.
López-Liria, Remedios, Sofía Vega-Tirado, María Á. Valverde-Martínez, Andrés Calvache-Mateo, Ana M. Martínez-Martínez, and Patricia Rocamora-Pérez. 2023. “Efficacy of Specific Trunk Exercises in the Balance Dysfunction of Patients with Parkinson’s Disease: A Systematic Review and Meta-Analysis.” *Sensors* 23 (4). https://doi.org/10.3390/s23041817.
Maher, Senan, Eoghan Donlon, Gerard Mullane, Richard Walsh, Tim Lynch, and Conor Fearon. 2024. “Treatment of Apathy in Parkinson’s Disease and Implications for Underlying Pathophysiology.” *Journal of Clinical Medicine* 13 (8). https://doi.org/10.3390/jcm13082216.
Mak, Margaret K., Irene S. Wong-Yu, Xia Shen, and Chloe L. Chung. 2017. “Long-Term Effects of Exercise and Physical Therapy in People with Parkinson Disease.” *Nature Reviews Neurology* 13 (11): 689–703. https://doi.org/10.1038/nrneurol.2017.128.
Mak, Margaret K.Y., and Irene S.K. Wong-Yu. 2019. “Chapter One - Exercise for

Parkinson's Disease." In *International Review of Neurobiology*, edited by Suk-Yu Yau and Kwok-Fai So, 147:1–44. Academic Press. https://doi.org/10.1016/bs.irn.2019.06.001.

———. 2021. "Six-Month Community-Based Brisk Walking and Balance Exercise Alleviates Motor Symptoms and Promotes Functions in People with Parkinson's Disease: A Randomized Controlled Trial." *Journal of Parkinson's Disease* 11 (3): 1431–41. https://doi.org/10.3233/JPD-202503.

Małgorzata Gaweł, Anna Potulska-Chromik. 2015. "Neurodegenerative Diseases: Alzheimer's and Parkinson's Disease" XXVIII (7).

Mee-inta, Onanong, Zi-Wei Zhao, and Yu-Min Kuo. 2019. "Physical Exercise Inhibits Inflammation and Microglial Activation." *Cells* 8 (7). https://doi.org/10.3390/cells8070691.

Mitchell, Alexandra K., Rebecca R. Bliss, and Frank C. Church. 2024. "Exercise, Neuroprotective Exerkines, and Parkinson's Disease: A Narrative Review." *Biomolecules* 14 (10). https://doi.org/10.3390/biom14101241.

Moratelli, Jéssica, Alicia Lima, Kettlyn Alexandre, Danielly Fausto, Aline Haas, and Adriana Guimarães. 2024. "Evidence of Physical Activity Interventions on Non-Motor Symptoms of People with Parkinson's Disease: An Umbrella Review." *Sport Sciences for Health* 20 (April):1–16. https://doi.org/10.1007/s11332-024-01197-6.

Morris, Huw R, Maria Grazia Spillantini, Carolyn M Sue, and Caroline H Williams-Gray. 2024. "The Pathogenesis of Parkinson's Disease." *The Lancet* 403 (10423): 293–304. https://doi.org/10.1016/S0140-6736(23)01478-2.

Mu, Lianwei, Jiajia Cai, Boya Gu, Laikang Yu, Cui Li, Qing-Song Liu, and Li Zhao. 2022. "Treadmill Exercise Prevents Decline in Spatial Learning and Memory in 3×Tg-AD Mice through Enhancement of Structural Synaptic Plasticity of the Hippocampus and Prefrontal Cortex." *Cells* 11 (2). https://doi.org/10.3390/cells11020244.

Ou, Ruwei, Yanbing Hou, Qianqian Wei, Junyu Lin, Kuncheng Liu, Lingyu Zhang, Zheng Jiang, et al. 2021. "Longitudinal Evolution of Non-Motor Symptoms in Early Parkinson's Disease: A 3-Year Prospective Cohort Study." *Npj Parkinson's Disease* 7 (1): 58. https://doi.org/10.1038/s41531-021-00207-5.

Padilha, Cristiano, Renan Souza, Fernando Schorr Grossl, Ana Paula Maihack Gauer, Clodoaldo Antônio de Sá, and Sinval Adalberto Rodrigues-Junior. 2023. "Physical Exercise and Its Effects on People with Parkinson's Disease: Umbrella Review." *PLOS ONE* 18 (11): e0293826. https://doi.org/10.1371/journal.pone.0293826.

Paillard, Thierry, Yves Rolland, and Philipe de Souto Barreto. 2015. "Protective Effects of Physical Exercise in Alzheimer's Disease and Parkinson's Disease: A Narrative Review." *J Clin Neurol* 11 (3): 212–19.

Palasz E, Niewiadomski W, Gasiorowska A, Wysocka A, Stepniewska A, Niewiadomska G. 2019. "Exercise-Induced Neuroprotection and Recovery of Motor Function in Animal Models of Parkinson's Disease" 10 (November). https://doi.org/10.3389/fneur.2019.01143.

Palasz, Ewelina, Adrianna Wysocka, Anna Gasiorowska, Malgorzata Chalimoniuk, Wiktor Niewiadomski, and Grazyna Niewiadomska. 2020. "BDNF as a Promising Therapeutic Agent in Parkinson's Disease." *International Journal of Molecular Sciences* 21 (3). https://doi.org/10.3390/ijms21031170.

Paolucci, T., S. Sbardella, C. La Russa, F. Agostini, M. Mangone, L. Tramontana, A. Bernetti, et al. 2020. "Evidence of Rehabilitative Impact of Progressive Resistance Training (PRT) Programs in Parkinson Disease: An Umbrella Review." *Parkinson's Disease* 2020 (1): 9748091. https://doi.org/10.1155/2020/9748091.

Petzinger, Giselle M, Beth E Fisher, Sarah McEwen, Jeff A Beeler, John P Walsh, and Michael W Jakowec. 2013. “Exercise-Enhanced Neuroplasticity Targeting Motor and Cognitive Circuitry in Parkinson’s Disease.” *The Lancet Neurology* 12 (7): 716–26. https://doi.org/10.1016/S1474-4422(13)70123-6.

Port, Rebecca J., Martin Rumsby, Graham Brown, Ian F. Harrison, Anneesa Amjad, and Claire J. Bale. 2021. “People with Parkinson’s Disease: What Symptoms Do They Most Want to Improve and How Does This Change with Disease Duration?” *Journal of Parkinson’s Disease* 11 (2): 715–24. https://doi.org/10.3233/JPD-202346.

Prieto-González, Pablo, and Fatma Hilal Yagin. 2024. “Energy Expenditure, Oxygen Consumption, and Heart Rate While Exercising on Seven Different Indoor Cardio Machines at Maximum and Self-Selected Submaximal Intensity.” *Frontiers in Sports and Active Living* 6. https://doi.org/10.3389/fspor.2024.1313886.

Ramirez, Elizabeth. 2024. “Influence of Aerobic Exercise on Stress Reduction in Philippines.” *International Journal of Physical Education, Recreation and Sports*. https://api.semanticscholar.org/CorpusID:270208833.

Rinalduzzi, Steno, Carlo Trompetto, Lucio Marinelli, Alessia Alibardi, Paolo Missori, Francesco Fattapposta, Francesco Pierelli, and Antonio Currà. 2015. “Balance Dysfunction in Parkinson’s Disease.” *BioMed Research International* 2015 (1): 434683. https://doi.org/10.1155/2015/434683.

Sharma, Neena K, Kristin Robbins, Kathleen Wagner, and Yvonne M Colgrove. 2015. “A Randomized Controlled Pilot Study of the Therapeutic Effects of Yoga in People with Parkinson’s Disease.” *International Journal of Yoga* 8 (1). https://journals.lww.com/ijoy/fulltext/2015/08010/a_randomized_controlled_pilot_study_of_the.11.aspx.

Silvia Paola Caminiti, Silvia Gallo, Federico Menegon, Andrea Naldi, Cristoforo Comi, and Giacomo Tondo. 2024. “Lifestyle Modulators of Neuroplasticity in Parkinson’s Disease: Evidence in Human Neuroimaging Studies.” *(Formerly Current Drug Targets - CNS & Neurological Disorders)* 23 (5): 602–13. https://doi.org/10.2174/1871527322666230616121213.

Singh, Richa, Walia Zahra, Saumitra Sen Singh, Hareram Birla, Aaina Singh Rathore, Priyanka Kumari Keshri, Hagera Dilnashin, Shekhar Singh, and Surya Pratap Singh. 2023. “Oleuropein Confers Neuroprotection against Rotenone-Induced Model of Parkinson’s Disease via BDNF/CREB/Akt Pathway.” *Scientific Reports* 13 (1): 2452. https://doi.org/10.1038/s41598-023-29287-4.

Skelton DA, Mavroeidi A. 2018. “Which Strength and Balance Activities Are Safe and Efficacious for Individuals with Specific Challenges (Osteoporosis, Vertebral Fractures, Frailty, Dementia)?: A Narrative Review” 1 (June). https://doi.org/10.22540/JFSF-03-085.

Souza, Jennyffer, Rodrigo A. da Silva, Débora da Luz Scheffer, Rafael Penteado, Alexandre Solano, Leonardo Barros, Henning Budde, Andrés Trostchansky, and Alexandra Latini. 2022. “Physical-Exercise-Induced Antioxidant Effects on the Brain and Skeletal Muscle.” *Antioxidants* 11 (5). https://doi.org/10.3390/antiox11050826.

Szuhany, Kristin L., Matteo Bugatti, and Michael W. Otto. 2015. “A Meta-Analytic Review of the Effects of Exercise on Brain-Derived Neurotrophic Factor.” *Journal of Psychiatric Research* 60 (January):56–64. https://doi.org/10.1016/j.jpsychires.2014.10.003.

Tolosa, Eduardo, Alicia Garrido, Sonja W Scholz, and Werner Poewe. 2021. “Challenges in the Diagnosis of Parkinson’s Disease.” *The Lancet Neurology* 20 (5): 385–97. https://doi.org/10.1016/S1474-4422(21)00030-2.

Vijiaratnam, Nirosen, Tanya Simuni, Oliver Bandmann, Huw R Morris, and Thomas Foltynie. 2021. “Progress towards Therapies for Disease Modification in Parkinson’s Disease.” *The Lancet Neurology* 20 (7): 559–72. https://doi.org/10.1016/S1474-4422(21)00061-2.

Vučcković, Marta G., Quanzheng Li, Beth Fisher, Angelo Nacca, Richard M. Leahy, John P. Walsh, Jogesh Mukherjee, Celia Williams, Michael W. Jakowec, and Giselle M. Petzinger. 2010. “Exercise Elevates Dopamine D2 Receptor in a Mouse Model of Parkinson’s Disease: In Vivo Imaging with [18F]Fallypride.” *Movement Disorders* 25 (16): 2777–84. https://doi.org/10.1002/mds.23407.

Zhou, Xiao, Peng Zhao, Xuanhui Guo, Jialin Wang, and Ruirui Wang. 2022. “Effectiveness of Aerobic and Resistance Training on the Motor Symptoms in Parkinson’s Disease: Systematic Review and Network Meta-Analysis.” *Frontiers in Aging Neuroscience* 14. https://doi.org/10.3389/fnagi.2022.935176.

Zou J, Hao S. 2024. “Exercise-Induced Neuroplasticity: A New Perspective on Rehabilitation for Chronic Low Back Pain” 17 (June). https://doi.org/10.3389/fnmol.2024.1407445.